DISCUSSION

These calculations have shown that misclassification of smokers as non-smokers, coupled with between-spouse smoking habit concordance, may cause an *apparent* increase in risk of lung cancer among non-smokers married to smokers similar to that observed epidemiologically. Several points arise: (a) the interviews were carried out in a non-emotive, non-health context. In the cotinine study, the subjects were unaware their answers were going to be verified; (b) bias may arise because of misclassification for any reason. In this study, data-handling errors were minimised by careful processing; (c) the increased concordance for heavier smokers may explain the higher observed risk of lung cancer seen in non-smokers married to heavy smokers; (d) in this study, for women, the increase in salivary cotinine associated with spouse smoking was about 0.2% of that associated with active smoking, making a 30% increase in lung cancer risk from passive smoking very unlikely.

It is concluded that most or all of the apparently increased risk of lung cancer in self-reported non-smoking women married to smokers is attributable to bias.

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MISCLASSIFICATION OF ENVIRONMENTAL TOBACCO SMOKE EXPOSURE: ITS POTENTIAL INFLUENCE ON STUDIES OF ENVIRONMENTAL TOBACCO SMOKE AND LUNG CANCER*

(Passive smoking; response bias)

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SUMMARY

The effects of selection, confounding, misclassification and bias must be eliminated from case-control studies of 'passive smoking' and lung cancer before a meaningful interpretation can be made. Misclassification includes the misclassification of the subject's non-smoking status, of the disease status or of the spouse's smoking habits. This paper shows that inflation of the amount smoked by the husbands of female lung cancer cases may have accounted for the apparent 'dose-response' relationships in 3 widely referenced case-control studies.

INTERPRETATION OF CASE-CONTROL RESULTS

Much of the literature on the association of 'passive smoking' with lung cancer consists of case-control studies of non-smoking women in which exposure to environmental tobacco smoke (ETS) from the husband's smoking is retrospectively estimated by interview of the subject or, if deceased, of a close relative or friend. Apparent 'dose-response' relationships are taken as supporting the claim that exposure to ETS increases the risk of lung cancer, i.e., a causal interpretation. This

paper considers the contribution which differential misclassification of exposure might make to these results.

Consider the stages leading to a subject's enrolment in one of these studies. A subject must first be a patient in the selected hospital or hospitals and agree to participate in the study. She must be listed in hospital records or tumor registries as having been diagnosed with the index disease for cases or controls and must satisfy specified demographic criteria with regard to sex, age (possibly) and marital status. In addition, each potential subject must have been listed in hospital records as a non-smoker [1] or be classified as one at interview (note that 40% of women with lung cancer, classified as 'non-smokers' in hospital records, had been smokers at some time or still were, whereas only 8.5% of non-smoking controls were similarly misclassified [1]). Next, the respondent must be selected. This may be the subject herself or her next of kin. The subject's exposure to ETS, usually from her husband, is estimated by interviewing the respondent. The interview may be structured and follow a carefully designed questionnaire or be relatively unstructured.

Each of these stages presents an opportunity for selection bias and misclassification errors to occur. A case-control study of female lung cancer and exposure to ETS therefore presents ample opportunity for artifacts to generate statistically significant results. In addition, confounding may also mimic 'dose-response' effects.

Biased selection of subjects and confounding

Cases, defined as currently married lifelong non-smoking female lung cancer patients, are rare and are not typical of the population. Their 'achieved status' [2] and that of the controls may introduce selection bias into the study. In addition, husband's smoking has been shown to be confounded with age, marital status, education, alcohol and marijuana use [3]. Husbands and wives share the same life style. ETS may therefore be a 'marker' for some other factor.

Misclassification

Misclassification of the subject's diagnosis, her smoking status or of her ETS exposure may occur. Thus, Weiss [4] highlights misclassification of the subject's disease status, her ETS exposure or both as possible explanations for the results found in the epidemiological literature. Misclassification has been shown to attenuate (i.e., underestimate) the true relative risk [5]. By converting to fixed end points, Kraemer [6] has shown that this is true for all measures of association, when misclassification is randomly distributed. Such results assume, however, that the misclassification occurs at the same rate and in the same direction in cases and controls. Misclassification of smoking wives as non-smokers is known to occur [7, 8]. If the wife of a smoker gives up smoking or denies smoking and is consequently misclassified as a non-smoker rather than an ex-smoker or current smoker, her subsequent lung cancer may be associated, in fact, with her smoking rather than

with her exposure to her husband's smoking. When hospital records are used to classify subjects, substantive misclassification is likely [9]. It has been reported [10] that, since husbands and wives tend to share smoking habits, as little as 5% misclassification among cases can produce a risk ratio of 1.42 in the absence of any effects whatever from exposure to ambient tobacco smoke.

Misclassification may also occur in classifying exposure to husband's smoking, especially if the next of kin responds for a deceased subject (more likely for lung cancer cases than for controls). The respondent is not 'blind', i.e., the respondent knows whether the subject has or had lung cancer or the 'control' disease. In this situation it is postulated that a respondent will tend to inflate the amount smoked by the husband for cases, but not for controls. This is called 'differential misclassification'. As epidemiologists have long recognised, 'when differential misclassification occurs (as in selective recall in case-control studies) the bias can be in either direction and can be great' [11].

METHODS

In the following we estimate the amount of differential misclassification required to mimic the reported results in 3 studies. It is noteworthy that in no study to date has the ETS exposure been measured directly. Rather, a coarse grouping of the amount smoked by the husband is used. This classification is derived from a respondent's answers to questions on the husband's long-term smoking habits, and is, in fact, only weakly associated with the ETS exposure of the non-smoking wife. In fact, 47% of currently non-smoking wives of smokers report less than 1 h per week ETS exposure in the home [3].

The estimation of differential misclassification rates from case-control studies requires an assumption to reduce the number of parameters. We assume that the classification of a case's 'exposure' is biased upwards and that there is no misclassification among controls. Here the husband's smoking habits are categorized so that $i = 0$ represents a non-smoker, $i = 1$ a light, occasional or ex smoker and $i = 2....m$ increasing amounts of smoking. Now let P_i, p_i represent the proportion of cases and controls, respectively, where the husband's smoking level is classified as $i = 0, 1$ to m, so that

$$\Sigma P_i = \Sigma p_i = 1$$

Then, if N, n are the number of cases and controls in the study, respectively, a regular 'dose-response' relationship between husband's smoking classification and lung cancer will have proportions $P_i P_j, p_i p_j$ such that, for all $i < j$,

$$\frac{P_i}{p_i} < \frac{P_j}{p_j}$$

Because individual cases are at risk of being misclassified, discrete steps of $1/N$ are

taken iteratively to find the minimum misclassification rate which will reproduce the 'dose-response' relationship reported in an individual study. The misclassification rates given below are found by reducing the exposure classification one case at a time until $P_i = p_i$ for all i, to the extent possible with discrete data.

RESULTS

3 case-control studies [1, 12, 13] report statistically significant trends in non-smoking women with lung cancer as the husband's reported smoking classification increases.

Thus, Garfinkel et al. [1] give a progression of odds ratios of 1.00, 1.15, 1.08 and 2.11 for 134 cases and 402 controls reportedly exposed to 0, <10, 10-20 and >20 cigarettes/day smoked by the husband at home. Pooling the intermediate categories gives increasing odds ratios of 1.00, 1.14 and 2.11 for exposures to 0, 1-19 (where 1-19 includes pipe or cigar) and >20 cigarettes/day. Correa et al. [13] give odds ratios of 1.00, 1.18 and 3.52 for reported exposures to 0, 1-40, and >40 pack-years smoked by the husband for 22 cases and for 133 controls. Trichopoulos et al. [12] give odds ratios of 1.00, 1.76 and 2.65 for the 3 exposure categories (non-, former and current smoker) in 40 cases and 149 controls.

Given the assumptions discussed above, Garfinkel's results can arise if 17 of the husbands of his 134 cases are misclassified upwards, a case misclassification rate of 13%. Correa's results can arise if 9 of his 22 cases' husbands are misclassified, a case misclassification rate of 41%. For Trichopoulos, the reported trend could have arisen from a case misclassification rate of 40%, i.e., if 16 of 40 cases' husbands were misclassified upwards. Because of the relatively larger number of cases in the first study [1], the overall case misclassification rate in the three studies required to reproduce the quoted results is 21%.

Although misclassification of exposure among cases has a disproportionate effect on the findings of these studies, another approach is to assume that the rates of misclassification are equal in cases and controls but in different directions. With this assumption, Garfinkel's results [1] can arise from a subject differential misclassification rate of 7%. Likewise, Correa's findings [13] may have arisen from a subject differential misclassification rate of 19%. A 20% overall differential misclassification rate will account for the trends reported by Trichopoulos in Tables 2 and 3 of his paper [12].

DISCUSSION

The findings of 3 case-control studies of lung cancer which show significant trends with 'exposure' to ETS can be generated by postulating differential misclassification of case exposure in the range of 13-40%. The significance of this finding rests on the validity of the underlying assumptions used in deriving these

rates of case or subject misclassification.

That misclassification exists in these studies is now widely accepted [3, 4, 9, 14-17]. In general, respondents are more likely to falsely inflate exposure if the case died of cancer than of some other disease [18].

More particularly, there is indirect evidence for the presence and effect of differential misclassification of exposure to ETS. For example, Garfinkel et al. [1] show that the effect of ETS exposure at home is null (an odds ratio of 1) when the case or her husband is the respondent; however, this null result is converted into an odds ratio of 3 when the son or daughter is the respondent.

Again, Table 3 of [15] suggests that differential misclassification may exist. This shows that 4 of 16 spouses of lung cancer cases (25%) contradicted the case by describing themselves as smokers whereas only 1 in 41 (2%) spouses of matched controls contradicted the control by describing themselves as smokers. Here there are two possible explanations. Either the case has denied her husband's smoking, or the husband has exaggerated his own smoking. In practice there is likely to be some behavior of each type. We assume however that this situation is indicative of inflation of the amount smoked by the husband when the case is the respondent.

The most recent case-control study of ETS and lung cancer [15], one which went to some pains to verify exposure classification, provided evidence suggesting a case misclassification rate of exposure as high as 25%. This figure may be compared to the 21% overall case misclassification rate required to produce the results in the 3 studies under review. Both figures may in turn be compared with a misclassification rate of 15% which Letzel and Johnson [19] found was required to invalidate a case-control study of ETS.
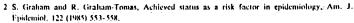
In summary, when a spouse's smoking status is used to estimate a non-smoker's ETS exposure, ' a considerable amount of misclassification' [3] may result. Since selection bias and confounding must also be considered, extreme caution is required in the interpretation of these studies. This is especially so when the literature as a whole contains several studies reporting no significant association between ETS exposure and lung cancer [15, 16, 20], as well as various inconsistencies, both among and within studies.

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